II. REMARKS

Preliminary Remarks:

Amendment of the Specification

The first paragraph of the specification is amended to update the priority of the present application.

The paragraph beginning on page 10, line 10, which describes the cDNA and amino acid sequences in Fig. 9 is amended to correctly identify the SEQ ID NO for the disclosed cDNA nucleotide sequence as SEQ ID NO: 4.

The paragraph beginning on page 22, line 1, is amended by rewriting the phrase "an antibody or an immunogenic fragment thereof," as "an antibody or an immunologically reactive fragment thereof, support for which is found on page 38, lines 8-9. One of skill in the art would recognize that the reference to "an immunogenic fragment thereof," in the original text was an obvious clerical error that is corrected by the present amendment.

Amendment of the Claims

Claims 15, 16, 18, and 19 are amended, claim 1-14, 17, and 20-33 are canceled, and new claims 34-36 are added.

Claim 15 is amended to be directed to a murine monoclonal antibody or immunologically reactive fragment thereof which recognizes and binds to a protein complex comprising a two-chain form of matriptase, wherein said antibody is selected from the group consisting of M32, M69, and M19. Support for the amendment is found in the specification, *e.g.*, on page 51, lines 22-24; and pages 90-91.

Claim 16 is amended to be directed to an isolated antibody or an immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of a matriptase of a human than to a single-chain (zymogen) form of matriptase of said human. Support for the amendment of claim 16 is found in the specification, *e.g.*, on page 25, lines 5-7, and at pages 90-91.

Claim 18 is dependent on claim 16 and specifies that the antibody is a monoclonal antibody, as described, for example, on page 89, line to page 90, line 1.

Claims 19 and 34 are dependent on claims 15 and 16, respectively, and specify that the immunologically reactive fragment is selected from the group consisting of scFv, Fab, Fab', and $F(ab')_2$, as described on page 38, lines 8-11.

Claim 35 is dependent on claim 16 and specifies that the single-chain form of matriptase comprises a polypeptide encoded by the nucleotide sequence of SEQ ID NO: 4, and the two-chain form of matriptase is produced by cleavage of said single-chain form of matriptase, support for which is found on page 63, lines 10-21.

Claim 36 is dependent on claim 16, and specifies that the antibody or immunologically reactive fragment thereof binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising a Kunitz-type serine protease inhibitor or a fragment thereof, as described, for example, on pages 90-91.

Patentability Remarks:

Objections to the specification

The official action objected to clerical errors in paragraphs on pages 10 and 22, which are corrected by the present amendment.

The official action also objected to the specification because it allegedly does not provide antecedent basis for the reference in claim 17 to a domain at positions 481-683 of the matriptase protein. Withdrawal of the objection is respectfully requested in view of the cancellation of claim 17.

35 U.S.C. §112, Second Paragraph

The official action rejected claims 15-19 under 35 U.S.C. §112, Second Paragraph, because the meaning of references to "an antibody or immunogenic fragment thereof" in the claims was considered to be unclear. Claims 15-19 are amended to refer instead to "an antibody or immunologically reactive fragment thereof," as suggested by the examiner.

The official action also rejected claims 17-20 under 35 U.S.C. §112, Second Paragraph, because references in claim 17 to positions 481-683 and to a transmembrane domain, and dependence of claims 17-20 on claim 14, was considered to render the claims indefinite. Claims 17 and 20 are canceled, and claims 18 and 19 are amended to depend,

respectively, on claims 16 and 15, which are both directed to an antibody or immunologically reactive fragment thereof.

Withdrawal of the rejection of claims 15, 16, 18, and 19, under 35 U.S.C. §112, Second Paragraph, is respectfully requested, in view of the amendments of the claims.

35 U.S.C. §112, First Paragraph

Claim 16 was rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, because the term "matriptase" is defined in the specification as "a trypsin-like protein, with a molecular weight of between 72-kDa and 92 kDa and is related to SEQ ID NO: 27 or is a fragment thereof." The examiner alleges that in view of the disclosed definition of matriptase, "claim 16 reads on any antibody that binds to SEQ ID NO: 27 or to any related protein thereto," and objects to the claim because the specification is not considered to provide "a number of examples sufficient so that in the art would recognize from the specification the scope of what is being claimed, " and alleges that the application does not describe antibodies that bind to matriptase of mammals other than a human. See pages 6-7 of the official action.

The applicants traverse this rejection, because the application clearly describes preparing antibodies against matriptase of mammals other than humans; *e.g.*, see pages 24-25. However, in the interest of expediting prosecution, claim 16 is amended to specify matriptase of a human. The applicants reserve the right to submit and prosecute claims directed to antibodies against matriptase of a non-human mammal in a later application continued from the present application.

The applicants further traverse the rejection of the claims under 35 U.S.C. §112, First Paragraph, as allegedly failing to comply with the written description requirement, because it is based on only a portion of the definition of matriptase that is taken out-of-context from the full definition of matriptase provided by the specification. The complete definition of matriptase provided by the specification includes a verbal description and a drawing that depict in detail the different molecular forms of matriptase that have been identified. The full definition of matriptase provided by the application at page 17, line 21, to page 15, line 5, is as follows:

> "By "matriptase" is meant a trypsin-like protein, with a molecular weight of between 72-kDa and 92-kDa and is related to SEQ ID NO: 27 or is a fragment

thereof. It can include both single-chain and double-chain forms of the protein. The zymogen form (inactive form) of matriptase is a single-chain protein. The two-chain form of matriptase is the active form of matriptase, which possesses catalytic activity. Both forms of matriptase are found to some extent in milk and cancer cells because extracellular matrix (ECM) remodeling is necessary to both normal and pathologic remodeling processes. Figure 14 displays all known forms of matriptase. Both cancer cells and milk contain the different forms of matriptase. However, in milk the dominant form is the activated form of matriptase which then binds to HAI-1."

The portion of the definition of matriptase quoted by the examiner does not include the information that "matriptase" as defined by the application can be either a single-chain form or a double-chain form of the protein. The full definition of matriptase describes the single-chain form "matriptase" as a zymogen; *i.e.*, an inactive precursor of an enzyme that require some change (*e.g.*, cleavage) to become active, and states that the two-chain form of matriptase is the catalytically active form of the matriptase protease. The definition further states that both cancer cells and milk contain the different forms of matriptase, and that the known forms of matriptase are displayed in Figure 14. Figure 14 graphically depicts the single-chain, zymogen form of matriptase as an uncomplexed protein, and the two-chain form of matriptase as either an uncomplexed protein, or as a protein present in a complex with a 50 kDa Kunitz-type inhibitor or a 40 kDa or 25 kDa fragment thereof.

To satisfy the written restriction requirement of 35 U.S.C. §112, First Paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations, using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. (Federal Register, Vol. 66, No. 4, January 5, 2001, page 1104).

As noted above, the full definition of matriptase provided by the application includes the depiction of known one-chain and two-chain forms of matriptase and matriptase complexes and identifies the amino acid sequence of a sample human matriptase polypeptide. The applicants submit that from the full definition of matriptase provided by the application, and the description of matriptase provided by the application as a whole, which teaches that

matriptase is present in human milk and human breast cancer cells (*e.g.*, see page 16, line 24 to page 17, line 3), one of skill in the art would recognize that the term "matriptase" as defined and used in the application excludes mammalian proteases other than the disclosed 92 kDa one-chain and two-chain forms of matriptase, exemplified by the disclosed human matriptase polypeptide having SEQ ID NO: 27, or 72-92 kDa fragments thereof. No evidence has been offered that suggests that any other proteases meet the full description of matriptase provided the application. The application describes techniques by which DNA molecules encoding variants of human matriptase proteins according to the claimed invention can readily be isolated from the human population, and persons of skill in the art would be familiar with additional, well-known methods by which such human matriptase proteins may also be isolated (see pages 24-25). In view of the foregoing, one of skill in the art would reasonably conclude that the inventor had possession of the invention of claim 16, and withdrawal of the rejection of claim 16 under 35 U.S.C. §112, First Paragraph, for lack of written description is respectfully requested

The rejection of claim 17 under 35 U.S.C. §112, first paragraph, is made moot by the cancellation of 17.

35 U.S.C. §102(b), 102(e), and 103(a)

Claims 15 and 16 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,482,848 of Dickson et al. Claim 18 was rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,482,848, or alternatively under 35 U.S.C. §103(a) as being allegedly being obvious in view of U.S. Patent No. 5,482,848. U.S. Patent No. 5,482,848 teaches making monoclonal and polyclonal antibodies against an 80 kDa metalloproteinase isolated from T-47D breast cancer cells, which is the active, two-chain form of matriptase.

Claims 15-18 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lin et al. (1997), which describes a rat monoclonal antibody (21-9) that binds to the 80 kDa form, and also to 95 kDa and 110 kDa forms, of matriptase isolated from T-47D breast cancer cells.

Claims 15-18 were similarly rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 6,077,938 of Dickson et al., which, like Lin et al. (1997),

describes a rat monoclonal antibody (21-9) that binds to the 80 kDa, 95 kDa, and 110 kDa forms of matriptase isolated from T-47D breast cancer cells.

Claims 15, 16, 18, and 19 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,972,616 of O'Brien et al., which describes preparing an antibody specific for TADG-15, a protein that has 99% sequence identity with human matriptase.

Claim 19 was rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of U.S. Patent No. 5,482,848, or U.S. Patent No. 6,077,938, or Lin et al. (1997), as applied to claims 15 and 16, or to claims 15-18, as discussed above, and further in view of U.S. Patent No. 5,084,266 of McKenzie et al. or U.S. Patent No. 5,516,637 of Huang et al. The latter two patents describe immunologically reactive fragments of antibodies such as Fab, Fab', and $F(ab')_2$, as being functional substitutes for whole antibodies.

The applicants submit that none of the references cited in the rejections under 35 U.S.C. §102(b), 102(e), and/or 103(a) stated in the official action describe the invention to which amended claims 15 and 16 and their dependent claims are directed, or suggest the claimed invention to one of ordinary skill in the art at the time of filing.

Independent claim 15 is amended to be directed to a murine monoclonal antibody that binds to a two-chain form of matriptase and is selected from the group consisting of M32, M69, and M19. Independent claim 16 is amended to be directed to an antibody or an immunologically reactive fragment thereof that selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human. The references cited in the stated rejections under 35 U.S.C. §102(b), 102(e), and 103(a) did not describe or suggest the possibility of isolating an antibody that selectively binds with greater affinity to the two-chain form of matriptase than to a single-chain (zymogen) form, as specified in claim 16. **Moreover, prior to the disclosure of such antibodies by the present application, it was not known and could not have been predicted by one of ordinary skill in the art that antibodies that selectively bind to the two-chain form of matriptase could be obtained.** Accordingly, withdrawal of the rejections of claims 15, 16, 18, and 19 under 35 U.S.C. §102(b), 102(e), and/or 103(a), is respectfully requested.

Double Patenting

Claims 15-18 were rejected for obviousness-type double patenting in view of claims 1-9 of U.S. Patent No. 6,077,938, which are directed to a composition containing monoclonal antibody 21-9.

Claims 15, 16, and 18 were rejected for obviousness-type double patenting in view of claims 4 and 5 of U.S. Patent No. 5,482,848 of Dickson et al., which are directed to a complex of an 80 kDa proteinase purified to homogeneity, to which is attached an antibody.

Claim 19 was rejected for obviousness-type double patenting in view of claims 1-9 of U.S. Patent No. 6,077,938, or claims 4 and 5 of U.S. Patent No. 5,482,848, further in view of either U.S. Patent No. 5,084,266 of McKenzie et al. or U.S. Patent No. 5,516,637 of Huang et al.

As discussed above, amended claim 15 and its dependent claims of the present application are directed to the specific murine monoclonal antibodies M32, M69, and M19, or to an immunologically reactive fragment thereof. Antibodies M32, M69, and M19 were not known at the time U.S. Patent Nos. 6,077,938 and 5,482,848 issued, and the claims directed to these antibodies are distinct from, and non-obvious in view of claims 1-9 of U.S. Patent No. 6,077,938, which specify antibody 21-9, or claims 4-5 of U.S. Patent No. 5,482,848, which specify an immune complex of an antibody and a purified 80 kDa proteinase, taken alone or in view of U.S. Patent No. 5,084,266 or U.S. Patent No. 5,516,637, which describe antibody fragments.

Also discussed above, amended claim 16 and its dependent claims of the present application are directed to an isolated antibody that selectively binds with greater affinity to a two-chain form of a human matriptase protein than to a single-chain form of the protein. At the time U.S. Patent Nos. 6,077,938 and 5,482,848 issued, it was not known that antibodies existed that were capable of selectively binding with greater affinity to a two-chain form of a human matriptase than to a single-chain form, and such antibodies are distinct from and non-obvious in view of claims 1-9 of U.S. Patent No. 6,077,938, which specify antibody 21-9, or claims 4-5 of U.S. Patent No. 5,482,848, which specify an immune complex of an antibody and a purified 80 kDa proteinase, taken alone or in view of U.S. Patent No. 5,084,266 or U.S. Patent No. 5,516,637, which describe antibody fragments. Accordingly, the applicants respectfully request that the stated rejections for obviousness-type double patenting be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date: May 27, 2005

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